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EXAMINER	
DELACROIX MUIRHEI, CYBILLE	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/756,890	KOEFFLER ET AL.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-60 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-60 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Claims 1-60 are presented for prosecution on the merits.

Claim Objection(s)

1. Claims 13, 41, 57 are objected to because of the following informalities: in claims 13, 41, 57, "5-fluoroceracil" should be deleted and replaced with –5-fluorouracil--. Appropriate correction is required.

Claim Rejection(s)—35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 2, 9-10, 12-14, 18, 20, 22, 24, 27, 29, 31, 33, 39, 41-42, 46, 48, 50, 52, 55, 57, 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of a limited number of cancers, does not reasonably provide enablement for all types of cancer embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The claims are drawn to methods for treating or reducing the recurrence of cancer by administering to a patient in need thereof paricalcitol or paricalcitol in combination with an anti-cancer agent.

(2) The state of the prior art

With respect to the term "cancer", this a broad term, which encompasses numerous forms of solid tumors, each involving different types of tissues and organs, as well as blood-borne tumors. As recognized in the art, many different anti-neoplastic drugs are used to treat a variety of cancers, but there is no one drug or one drug combination, which is capable of treating all cancers in general. Please see pages 1226-1229 of Goodman & Gilman's.

(3) The relative skill of those in the art

The relative skill of those in the art is high. However, given the state of the art as set forth above, the artisan is currently unaware of any one particular anticancer agent or combination of agents that is effective against all cancer cell types.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical and cancer art is high. Additionally, the lack of significant guidance from the present specification or prior art with regard to the actual treatment or reduction in recurrence of all cancer cell types in a mammal, including a human, with the claimed compound or combination of compounds as the active ingredient(s) makes practicing the claimed method unpredictable.

(5) The breadth of the claims

The complex nature of the subject matter to which the present claim is directed is exacerbated by the breadth of the claim. The claims are broad and encompasses treatment of a vast number of possible cancer types including solid and blood-borne tumors.

(6) The amount of direction or guidance presented

Applicant's specification appears to only be enabled for the treatment of a limited number of cancers such as leukemia, myeloma, colon cancer, breast cancer. It does not enable one of ordinary skill in the art to use the claimed invention in the treatment of all cancer cell types covered by the term "cancer." Applicant's specification does not set forth a representative number of examples of cancers, which would be treated by the claimed compound or combination of compounds.

(7) The presence or absence of working examples

The specification provides in vitro and in vivo examples using breast, brain, colon, leukemia, myeloma, lymphoma and endometrial carcinoma cell lines. Please see pages 56-80.

(8) The quantity of experimentation necessary

Since (1) the prior art recognizes that no one compound or combination of compounds is capable of treating the vast number of possible solid or blood borne tumors encompassed by the term "cancer"; (2) the specification shows anti-tumor activity only against a limited number of tumor cell types; and (3) since the claims are very broad and include treatment or reduction in recurrence of any type of cancer, solid or blood-borne, one of ordinary skill in the art would be burdened with undue experimentation to determine which cancers would be treated or whose recurrence would by reduced by administration of the claimed compound or combination

compounds.

Claim Rejection(s)—35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 2, 4 are rejected under 35 U.S.C. 102(b) as being anticipated by DeLuca et al., EP 0 387 077.

DeLuca et al. disclose methods for treating psoriasis, malignant cells (neoplastic disease), leukemia and primary or secondary hyperparathyroidism, wherein the methods comprise administering an effective amount of 1α,25-Dihydroxy-19-nor-vitamin D_2 (i.e. paricalcitol). Please see the abstract; page 8, lines 14-24; example 3; claims 19-24.

Claim Rejection(s)—35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 3, 5-8, 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLuca et al., supra.

DeLuca et al. as applied above.

DeLuca et al. do not disclose treatment of the specific leukemias, myelodysplastic syndrome or breast or colon cancer as claimed by applicant; however, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer 1α,25-Dihydroxy-19-nor-vitamin D_2 (i.e. paricalcitol) to a patient suffering from these specific cancers because DeLuca et al. teach that 1α,25-Dihydroxy-19-nor-vitamin D_2 significantly inhibits the proliferation of malignant cells and one of ordinary skill in the art would reasonably expect 1α,25-Dihydroxy-19-nor-vitamin D_2 to inhibit the proliferation of malignant cells such as the specific leukemias, breast or colon cancer cells.

Furthermore, it would have been obvious to one of ordinary skill in the art to administer 1α,25-Dihydroxy-19-nor-vitamin D_2 to an individual in cancer remission, because one of

ordinary skill in the art would reasonably expect 1α,25-Dihydroxy-19-nor-vitamin D_2 to significantly inhibit newly developed malignant cells thereby reducing the likelihood of cancer recurrence in the patient.

5. Claims 9-32, 39-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLuca et al. in view of Aggarwal US2004/0058021 and WO 2004/043374 ('374) (102(e)=11-2002) and Salcedo et al., US2005/0129616 (102(e)=05-2001).

DeLuca et al. as applied above.

DeLuca et al. do not disclose treating the neoplastic disease, leukemia, malignancy or reducing the recurrence of such diseases with 1α,25-Dihydroxy-19-nor-vitamin D_2 (i.e. paricalcitol) in combination with another anti-cancer agent as claimed by applicant. However, the examiner refers to (1) Aggarwal, which teaches that PS341 has been used in the treatment of multiple myeloma [0038]; (2) WO '374, which discloses methods of inhibiting the growth of cancer cells by administering an effective amount of the proteasome inhibitor PS341 (please see the abstract; page 7) and (3) Salcedo et al., which disclose known chemotherapeutic agents taxol [0017], methotrexate, 5-fluorouracil, daunomycin [0329], adriamycin [0484], arsenic trioxide, dexamethasone [0487].

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify DeLuca's method to treat malignancies or neoplastic diseases by administering 1α,25-Dihydroxy-19-nor-vitamin D_2 in combination with the known anticancer agents taught by Salcedo et al. as well as PS341 as taught by Aggarwal and WO '374 because one of ordinary skill in the art would reasonably expect the at least additive effect of the

combination of compounds to inhibit cancer cell proliferation thereby treating the neoplastic disease.

Concerning the treatment of the specific leukemias, myelodysplastic syndrome, multiple myeloma, prostate or breast or colon cancer as claimed by applicant, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer 1α,25-Dihydroxy-19-nor-vitamin D_2 in combination with known anti-cancer agents to a patient suffering from these specific cancers because DeLuca et al. teach that 1α,25-Dihydroxy-19-nor-vitamin D_2 significantly inhibits the proliferation of malignant cells and one of ordinary skill in the art would reasonably expect 1α,25-Dihydroxy-19-nor-vitamin D_2 in combination with the known anti-cancer cells to inhibit the proliferation of malignant cells found in leukemias, myeloma, prostate, breast or colon cancer cells.

Furthermore, it would have been obvious to one of ordinary skill in the art to administer 1α,25-Dihydroxy-19-nor-vitamin D_2 in combination with an anti-cancer agent to an individual in cancer remission, because one of ordinary skill in the art would reasonably expect 1α,25-Dihydroxy-19-nor-vitamin D_2 and the anti-cancer agent to significantly inhibit newly developed malignant cells thereby reducing the likelihood of cancer recurrence in the patient.

Conclusion

Claims 1-60 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Cybille Delacroix-Muirheid** whose telephone number is **571-**

272-0572. The examiner can normally be reached on Mon-Thurs. from 8:30 to 6:00 as well as every other Friday from 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Christopher Low**, can be reached on **571-272-0951**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM
Oct. 3, 2005

Cybille Delacroix-Muirheid
Patent Examiner Group 1600